REMARKS

This Amendment is being submitted in response to the Office Action mailed on March 14, 2007 in connection with the above-identified application. Reconsideration of the above-identified application in view of the following arguments is respectfully requested.

STATUS OF CLAIMS

Claims 1-10 are rejected and are the subject of this response.

STATUS OF AMENDMENTS

There have no amendments made to the claims or specification.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to liquid dosage forms of proton pump inhibitors. Specifically, the present invention relates to liquid dosage forms of proton pump inhibitors (PPIs) that comprise micro-granules of an enterically coated PPI and a liquid suspension vehicle.

It is well known that many pharmaceutical compounds are susceptible to acidic degradation (hereinafter referred to as "acid labile drugs"). In order to overcome pH sensitivity, acid labile drugs are typically administered in a form that protects the drug from the acidic environment, such as a protective enteric coating. Enterically coated capsules or tablets are one of the most widely used methods of administering acid-labile drugs to patients, but are difficult to administer to patients that have difficulty

swallowing, such as pediatric or critically ill patients. Moreover, it is difficult to administer partial dosage forms of acid-labile drugs in an accurate and a consistent manner when necessary. Accordingly, there is a need for a liquid dosage form of a PPI that 1) maintains the efficacy of the active components, 2) is easily administered to patients whom have difficulty swallowing, and 3) can be dispensed in an accurate, titratable dosage.

As mentioned above, the present invention is directed to formulations that comprise enterically-coated micro-granules and a liquid suspension vehicle having a pH less than 6.0 and a viscosity sufficient to uniformly suspend the micro-granules for a sufficient time to dose titrate the bulk suspension of micro-granules. Applicants were the first to develop a formulation that allowed a dose titratable amount of enterically-coated micro-granules to be administered to a patient. The viscosity of the formulation ensures that the micro-granules are homogenously suspended for a time sufficient to titrate a complete or fractional dosage for administration to a patient.

REMARKS TO OVERCOME THE REJECTIONS

Rejection of Claims 1, 2, and 5 Under 35 U.S.C. §102(a) and §102(e) as being anticipated by WO 02/45692

Claims 1, 2, and 5 are rejected under 35 U.S.C. §102(a) and §102(e) as being anticipated by WO 02/45692 (hereinafter "WO '692"). The Examiner asserts that WO '692 discloses compositions comprising acid labile drugs, specifically proton pump inhibitors in a suspension to be administered to a patient in need thereof. The Examiner further asserts that WO '692 teaches that is known to coat these oral dosage forms of acid

labile ingredients with enteric coating (See page 3 of the Office Action). Moreover, the Examiner suggests that the reference teaches providing a juice or suspension for the oral administration of the acid labile active agent and that such dosage form is in the form of a powder and prior to administration is combined with the liquid vehicle (See page 3 of the Office Action). The Examiner take the position that the composition would have the desired pH and a viscosity sufficient to form a suspension. (See page 4 of the Office Action). Applicants respectfully traverse this rejection.

Applicants respectfully submit that WO '692 does not disclose or suggest Applicant's invention. In particular, the "Background" section of WO '692 discloses that there are many problems associated with the prior art coatings of acid labile drugs, in particular enteric coatings. As the Examiner suggests, WO '692 merely recognizes that "it is known to coat these oral dosage forms of acid labile ingredients with enteric coatings". In particular, the "Background" of WO '692 discusses the problems associated with the use of enteric coatings, such as the need for thick intermediate layers between the active ingredients and the enteric coating, as well as the considerable effort needed to avoid traces of moisture during production (see page 2, 1st paragraph of WO '692). Accordingly, WO '692 discloses and explains all of the problems associated with the use of enteric coatings and teaches a composition that does not use an enteric coating.

In particular, the compositions of WO '692 comprise an aqueous base, an excipient, a thickener and a matrix composed of at least one paraffin (See, WO '692, page 3, first full paragraph). WO '692 specifically discloses that its compositions do not comprise enteric coatings. More particularly, WO '692 states,

> [I]t is an object of the present invention to provide a juice (hereinafter also referred to as suspension) for the oral administration of acid-labile active ingredients which can be produced without great technical complexity, which is stable and not sensitive to moisture and displays good controllability of active ingredient delivery. It ought also be possible to produce the suspension ready for use. Another object of the invention is also to provide a suspension for the oral administration of acid-labile active ingredients, *where it is unnecessary to protect the acid-labile ingredient by an enteric coating*. (*emphasis added*).

(See bottom of page 2, last paragraph through line 1-3 of page 3)

> The pharmaceutical preparation of the invention can be produced without great technical complexity. Technically complicated processes for applying enteric layers and intermediate layers are unnecessary.

(See bottom of page 3, last full paragraph)

The Examiner further suggests that WO '692 discloses several examples of polymers which are conventionally used to make enteric coating compositions and that the "resistance to gastric juice" as mentioned on page 8 of WO '692 is an inherent property of enteric coatings (See page 8 of Office Action). WO '692 specifically provides that that the object of the invention "can be achieved by a pharmaceutical preparation where a plurality of individual active ingredient units *are dispersed in a thickened base composed of one or more pharmaceutical excipients*" (*emphasis added*, See page 3, 2nd and 3rd paragraphs) of WO '692. Moreover, WO '692 provides that the mixtures in the individual active ingredient units may include one or more other pharmaceutically suitable excipients, such as polymers. WO '692 states that "It is possible by adding suitable polymers, for example, to influence the pharmaceutical properties of the individual active ingredient units (e.g. delivery of the active

ingredients)" (See page 6, 3rd full paragraph, last sentence). There is no mention of the use of these polymers in the form of an enteric coating. Per the disclosure, the polymers, provided as excipients, are *only* dispersed in a thickened base and not as an enteric coating. Although WO '692 suggests that the suspension can be processed without losing functionality (such as resistance to gastric juice), there is no support that such performance is achieved through the use of an enteric coating. Furthermore, based on the objects of the invention previously discussed above, the purpose of WO '692 is to avoid the use of enteric coatings.

In contrast, the claimed invention requires that the micro-granules be coated with an enteric coating.

According to the *Manual of Patenting Examining Procedure* Section 2131 (8th Edition August 2005 Revision), a claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Therefore, because WO '692 does not teach each and every element of the claimed invention, this reference does not anticipate claims 1, 2 and 5. Thereupon, these rejections should be withdrawn.

Rejection of Claims 1-11 Under 35 U.S.C. §103(a) as being obvious over WO 02/45692 and WO 94/25070 in view of WO 02/45692

Claims 1-9 are rejected under 35 U.S.C. §103(a) as being obvious over WO 02/45692 (WO '692) and over WO 94/250070 (the '070 application) in view of WO 02/45692. Applicants respectfully traverse the rejection.

a) Rejection over WO '692

The Examiner states that WO '692 discloses that it is known to coat acid labile drugs with enteric coatings. As previously addressed, WO '692 merely discloses that this is generally known in the "Background" section, while going on to explain that there are many problems associated with prior art enteric coatings of acid labile drugs. The actual compositions disclosed in WO '692 do not contain an enteric coating, as WO '692 was seeking to avoid the problems associated with such coatings by using a different formulation. (See the Applicants' discussion of the §§102(a) and (e) rejections above).

The Examiner cites Example 6 and Example C of WO '692 and argues that "it would have been obvious to one of ordinary skill in the art to provide a suspension with the specific pH requirements such that the enterically coated microgranules would not dissolve in the liquid vehicle, but would form a suspension. As example C discloses that in the suspension a desirable swelling is achieved this would leave one of ordinary skill in the art to expect that the solution is in a pH range sufficiently low to prevent the degradation of the enterically coated microgranules." (See, the Office Action, page 5-6). The Examiner further deducts that "it would be obvious to one of ordinary skill in the art to adjust the thickening ingredients in the composition to achieve the desired viscosity to suspend the micro-granules of lansoprazole" (See, the Office Action, page 6).

Applicants respectfully traverse this rejection.

As Applicants explained above, WO '692 discloses acid labile drug compositions in a paraffin matrix, not with an enteric coating. These compositions are very different from the compositions claimed by Applicants. Specifically, Example 6 of WO '692 discloses how to prepare a matrix composition. Example C discloses how to make a

suspension of the matrix composition prepared according to Example 6. Since the matrix composition of Example 6 is significantly different from the compositions claimed in the instant invention (namely, the compositions of WO '692 use a paraffin wax rather than an enteric coating), a suspension of Example C is also very different from Applicants' presently claimed compositions.

More specifically, as discussed in the *Handbook of Pharmaceutical Excipients*, 4th edition, Eds. Rowe, R.C., Sheskey, PJ and Weller, PJ (Pharmaceutical Press), paraffins are purified mixtures of solid saturated hydrocarbons that are obtained from petroleum or shale oil. Paraffins are practically insoluble in water and are stored at temperatures of not more than 40°C. Functionally, paraffins are used as a base for ointments and as stiffening agents. Paraffins are included in the FDA's Inactive ingredients Guide and are used in oral capsules and tablets and topical emulsions and ointments.

The compositions of the present invention require that the acid-labile drug is coated with an enteric coating. Thereupon, the release of the acid-labile drug is delayed until the composition reaches the small intestine. In contrast, additionally, the compositions of WO '692 will be subjected to acid degradation and drug release in the stomach. Moreover, the compositions of the present invention are liquid formulations that can be administered via feeding tubes to patients in need of treatment thereof. As mentioned above, paraffins are temperature sensitive and are stored at temperatures of not more than 40°C. In fact, because of this temperature sensitivity, the compositions described in WO '692 would be very difficult to administer via a feeding tube as these compositions could potentially clog and block the tube, thus leading to obvious safety

concerns for the patient. Moreover, the performance of compositions containing paraffins would be temperature dependent. Specifically, if the formulation of such compositions are varied by a few degrees, the release of the drug as well as the protection of the composition from acid degradation in the stomach, will be greatly varied. Thus, the pharmacokinetic profiles of the composition as described in WO '692 will be very different that the pharmacokinetic profiles of the compositions of the present invention.

The compositions of the present invention provide a number of advantages. Specifically, these compositions can be titrated to provide varying doses (such as 2 mg, 5 mg, 8 mg, etc.). Additionally, uniform dosing can be provided to a patient. Titration of the compositions containing the paraffin matrix described in WO '692 is not possible. Moreover, given the nature of these compositions, it would be difficult to provide uniform dosing as with the compositions of the present invention. Therefore, in summary, compositions containing paraffins and compositions containing enteric coatings are very different compositions.

Applicants submit that it would not be obvious to one skilled in the art to replace the matrix disclosed in Examples 6 and C with an enteric coating. Similarly, the claimed kits of the present invention are also not obvious over the compositions disclosed in WO '692 since any kit comprising the components of WO '692 would comprise a matrix containing at least a paraffin wax and would not comprise an enteric coating. In fact, WO '692 actually teaches away from the use of enteric coatings because of the problems associated with these coatings and suggests compositions that do not contain enteric coatings.

Therefore, Applicants submit that claims 1-9 are not obvious under 37 U.S.C. §103(a) over the compositions disclosed in WO '692.

b) Rejection over WO 94/25070 in view of WO 04/45692

The Examiner states that WO '070 teaches a pharmaceutical composition for oral administration to animals comprising a proton pump inhibitor in the form of beads that are enterically coated and incorporated with a pH buffer into water or a water solution (See, Office Action, page 6). The Examiner further states that the pH buffer is used to decrease the pH of the solution to 5.5 or below and that this reference also teaches making a kit comprising the dry enteric coating beads. The Examiner admits that WO '070 does not teach the viscosity requirement or making microparticles of the proton pump inhibitor. However, the Examiner claims that WO '692 cures this deficiency. *Id.* According to the Examiner, one of ordinary skill in the art would have been motivated to make microparticles because microparticles make a more uniform suspension. One of ordinary skill in the art would have been motivated to make a solution with a viscosity that is suitable to suspend the micro-granules, and would look thus to WO '692 that teaches that by adding thickening agents the desired viscosity can be achieved" (See, Office Action, page 7).

Applicants respectfully disagree. First, WO '070 does not disclose or suggest compositions comprising a liquid vehicle as recited in the claims of the instant application. Rather, WO '070 discloses paste-like gel compositions comprising proton pump inhibitors (See, WO '070, page 3). By definition, paste-like gel compositions are different from liquid compositions. Specifically, as shown discussed in *Remington, The*

Science and Practice of Pharmacy 21st Edition (hereinafter "Remington"), which is attached herewith, the USP defines pastes as semisolid dosage forms that contain one or more drug substances intended for topical application. As discussed further in Remington, "[P]astes adhere reasonably well to the skin and are poorly occlusive. For this reason, they are suited for application on or around moist lesions. The heavy consistency of pastes imply a degree of protection and may, in some instances, make the use of bandages unnecessary." With respect to gels, as discussed in Remington, gels are semi-rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules in the dispersed phase (See Remington, page 770). As further discussed by Remington and pursuant to the USP, gels are used to administer drugs topically or into body cavities. *Id.*

The Examiner suggests that Claim 6 of WO '070 comprises a liquid vehicle due to the incorporation of dry mixture into water or a water solution (See, Office Action, page 10). Claim 6 of WO '070 specifically provides for a pharmaceutical composition "wherein dry enteric-coated beads or tablets of a proton pump inhibitor, dry gelling agent(s) and optionally pH-buffering and/or flavouring substances are mixed to a dry mixture before the addition of water or a water solution" (See, WO' 070, page 12, Claim 6). Moreover, the detailed description of WO '070 specifically provides that "...when water is added to this mixture a past-like gel is formed" (See, WO '070, page 3, lines 11-12). There is no suggestion that the addition of water or a water solution is used to form a liquid vehicle as indicated by the Examiner. In contrast, the dry gelling agent(s) provided in Claim 6 are combined with water to create a paste-like gel as required by the

invention for administration to animals. Any other type of suspension, would render the use of the '070 invention useful for its suggested purpose as disclosed throughout the application and discussed above.

Additionally, as discussed above, the compositions of the present invention provide a number of advantages. Specifically, these compositions can be titrated to provide varying doses and uniform dosing can be provided to a patient in need of treatment. Titration of the compositions containing paste-like gel compositions as described in WO '070 is not possible. Moreover, given the nature of these compositions it would be difficult to provide uniform dosing. Thereupon, there is no suggestion or motivation, in either WO '692 or WO '070 to modify the paste-like gel composition of WO '070 to a liquid form.

WO '692 does not cure the deficiencies of WO '070. Contrary to the Examiner's position, and as previously discussed in detail above, WO '692 does not teach coating the compositions with enteric coatings. As explained above, WO '692 only discloses that some prior art compositions utilized enteric coatings. It does not disclose or suggest that the prior art compositions comprised microgranules or that prior art compositions comprised a liquid vehicle having a pH less than 6.0. On the contrary, WO '692 teaches away from Applicants' invention by pointing out the various problems associated with the prior art compositions. As discussed several times herein, WO '692 teaches away from compositions containing enteric coatings. Moreover, as also discussed previously herein, the compositions disclosed in WO '692 require the use of a paraffin matrix. The

paraffin matrix of the compositions in WO '692 are very different compositions than the compositions of the present invention which use an enteric coating.

Therefore, while WO '692 discloses that some prior art acid labile compositions comprise enteric coatings, it does not suggest or motivate a person skilled in the art to modify the compositions of WO '070 to arrive at the Applicants' claimed compositions, namely, compositions comprising microgranules with enteric coatings, a liquid suspension vehicle having a pH less than 6.0 and having a viscosity sufficient to suspend the microgranules. To the contrary, WO '692 actually teaches away from such a modification.

In summary, the compositions of WO '692 and WO '070 are significantly different from Applicants' claimed compositions. WO '070 discloses paste-like gel compositions that do not comprise microgranules. WO '692 discloses suspensions, which while seeking to avoid the problems with enteric coatings, do require a matrix that comprises at least a paraffin. Thereupon, there is nothing in WO '692 and WO '070, either individually, or collectively, which discloses or suggests the claimed invention. Therefore, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and that the rejection of claim 1-9 as being obvious over WO '070 in view of WO '692 should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 102 and 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 04-2223.

DykEMA**G**OSSETT PLLC
10 South Wacker Drive, Suite 2300
Chicago, Illinois 60606 USA
(312) 876-1700
(312) 627-2302 (facsimile)
www.dykema.com
ipmail@dykema.com

Respectfully submitted,

s/Lisa V. Mueller

Lisa V. Mueller
Attorney for Applicant
Registration No. 38,978

Date: July 11, 2007

Direct telephone calls to: 312.627.2184

BH01\764192.1
ID\MMGG